

Amendments to the Specification

Please add the following paragraph after the title on Page 1:

This application claims the benefit of the filing date of U.S. Application Serial No. 09/942,117 filed August 30, 2001 which claims the benefit of German Application No. 10045803.3 filed September 7, 2000 and German Application No. 10123/33.4-41 filed May 20, 2001.

Please delete the paragraph on page 4, lines 16-25, and replace it with the following paragraph:

--The ED_b domain is a repetition sequence of type III that comprises 91 amino acids and has an extremely high sequence homology between the rat and chicken fibronectin, which is between 96% and 100%. No RGDS (SEQ ID NO: 5) sequences or other amino acid sequences occur within the domains, of which it is known that they mediate an interaction with integrins. The specific function of the ED-B domain is unknown up until now. Three studies have been published that conduct speculations on a general stimulating function with respect to adhesion/cell propagation for various cells.--

Please delete the paragraph on page 6, line 17 through page 7, line 26 and replace it with the following paragraph:

--The study by Chen and Culp (1998, aaO) shows that the mono-repetition protein ED_b was more heavily promoted for the propagation of BALB/c 3T3 cells as well as for inducing FAK-tyrosine phosphorylation than the adjacent repeats III₈, etc. The assumption is advanced that in the case of physiological concentrations of cellular fibronectins, the binding of the tetrapeptide RGDS (SEQ ID NO: 5) from III₁₀ to the integrins possibly produces a signal of inadequate strength for the cell adhesion, so that no tyrosine-phosphorylation response arises from the interaction between III₁₀ and integrin-mediated mechanisms. It is further assumed that the difference with respect to the response to the various mediated cell adhesions is produced by a varying activation of various small GTP-binding proteins. Three of these proteins -- cdc42, rac and rho -- which all are members of the ras-superfamily, play important roles in the case of cell-morphological changes. cdc42 acts sequentially upstream from rac and directly induces the appearance of filopodia (Nobes, C. D. and

Hall, A., 1995, Rho, rac and cdc42 GTPases Regulate the Assembly of Multimolecular Focal Complexes Associated with Actin Stress Fibers, Lamellipodia and Filopodia, **Cell**. **81**, 53-62). The activation of rac is then responsible for the formation of lamellipodia and the network of actin filaments between the filopodia. Further downstream, rho can be activated by rac and induces focal adhesion and actin stress fibers. All of these events depend on the activation of tyrosine kinase, and it is assumed from FAK that it is involved in these processes. Chen and Culp make the conjecture that the morphological differences between cells that are adherent via 7-ED_b-8 as well as cells that are adherent via 8-9-10 are based on the varying activation of the small GTP-binding proteins. The above suggests that an adhesion via 8-9-10 via the integrin-mediated signal path finally leads to an activation of rho to produce focal adhesions and actin stress fibers, while the adhesion of BALB/c-3T3 cells via 7-ED_b-8 leads only to an activation of cdc42 proteins and rac proteins, but does not activate rho. For the above-mentioned speculations, however, data are presented in neither of the two studies.--

Please delete the paragraph on page 20, lines 24 to 25, and replace it with the following paragraph:

-- **Fig. 6** shows the partial sequences (SEQ ID NOs:1-4 and 6-22) of the synthetic peptides from the ED_b-fibronectin domains used in Fig. 5;--

Please delete the paragraph on page 28, lines 8 to 11, and replace it with the following paragraph:

-- **Fig. 6** shows the partial sequences (SEQ ID NOs:1-4 and 6-22) of the synthetic ED-B peptides with the selected sequence designations that are removed from the total sequence of the ED_b-fibronectin domains. The one character code for the amino acids is used.--

Replace the paragraphs beginning on page 31, line 26 to page 32, line 25 with the amended paragraphs below.

--For the covalent coupling of proteins to ~~sepharose~~ SEPHAROSE, the following process was selected:

Material: Activated CH ~~sepharose~~ SEPHAROSE 4 B Pharmacia Biotech, Code No. 17-0490-01

1 mmol of HCl, 2.2% NaHCO₃

Method: The HCl is cooled in an ice bath, the ~~sepharose~~ SEPHAROSE is allowed to heat to room temperature.

Then, the ~~sepharose~~ SEPHAROSE is washed with 1 mmol of HCl. 10 ml of HCl is required per ml of ~~sepharose~~ SEPHAROSE. The ~~sepharose~~ SEPHAROSE is allowed to trickle slowly into the precooled tube, where it then swells for about 15 minutes. (1 g of ~~sepharose~~ SEPHAROSE corresponds to 3 ml of swollen ~~sepharose~~ SEPHAROSE.) Then, the tube is centrifuged for 1 minute at 800 U. The supernatant is pipetted off and discarded. This process is repeated three times.

After the third washing, HCl is again added, the tube is swung around and centrifuged for 3-5 minutes at 800 U. The supernatant is pipetted off, and the pellet is dissolved with 20 ml of millipore water and transferred into two new centrifuging tubes (1 tube each for 7-EDB-8-9 ~~sepharose~~ SEPHAROSE and for 7-8-9 ~~sepharose~~ SEPHAROSE, i.e., ~~sepharose~~ SEPHAROSE to which a polypeptide with repeats III7, ED b, III8 and III9 or III7, III8 and III9 is coupled). The tubes are again centrifuged off immediately, the supernatant is pipetted off, and 1-5 mg of protein/ml of ~~sepharose~~ SEPHAROSE can be coupled.

(i.e., 2 mg of protein/ml of ~~sepharose~~ SEPHAROSE 7-8-9

2 mg of protein/ml of 7-EDB-8-9)--

Replace the paragraph on page 33, lines 5-7 with the amended paragraph below.

--To determine the protein concentration, which is to be used in the covalent coupling to ~~sepharose~~ SEPHAROSE, a Bradford test was carried out:--

Replace the section on page 33, lines 19-20 with the amended section below.

--Material: Activated CH ~~sepharose~~ SEPHAROSE 4B Pharmacia Biotech, Code No. 17-0490-01--